Remarks

The Specification of the above-captioned application has been amended. Claims 1-58 and 70-117 have been cancelled without prejudice to pursuing them in a continuing application. Claims 60 and 68 have been amended to correct inadvertent clerical errors and not for reasons related to patentability. The Specification and claims 60 and 68 have been amended in response to a requirement of form expressly set forth for the first time in the Final Office action. Accordingly, Applicants respectfully request entry thereof pursuant to 37 CFR 1.116(b)(1). No new matter has been added.

Applicants respectfully request entry of this Amendment after Final as it serves to comply with issues raised for the first time in the Final Office action, decrease the number of issues for appeal, cancel rejected claims and to present rejected claims in better form for consideration on appeal pursuant to 37 CFR 1.116(b)(1) and (2).

Applicants thank the Examiner for his helpful suggestions regarding the need for a Sequence Listing in paper and computer readable form. To fulfill the requirements of 37 CFR §1.821-1.825, Applicants submit herewith an initial Sequence Listing in PDF form, as required by 37 CFR §1.823(a), and in computer readable form, as required by 37 CFR §1.824. Pursuant to 35 CFR 1.821-1.825, I hereby state that the content of the paper and computer readable copies of the Sequence Listing submitted herewith and in accordance with 37 CFR §§1.821(f) and (g), respectively, are the same and include no new matter. A copy of the Notice to Comply is also submitted herewith.

Applicants submit that the Amendment to page 1 of the above-captioned application renders moot the Examiner's objection (set forth at page 4 of the April 26, 2007 Office action) to the priority claim.

Applicants submit that the attached sequence listing renders moot the objection to page 31 of the Specification of the above-captioned application.

Applicants thank the Examiner for kindly indicating that claim 68 would be allowable if amended to correct an inadvertent clerical error. Applicants submit that claim 68 as amended is now allowable.

Applicants submit that the amendment to claim 60 renders moot the rejection of claim 63 under 35 U.S.C. § 112, second paragraph, and respectfully request that it be withdrawn.

Claims 132-137 stand rejected under 35 U.S.C. § 112, first paragraph.

As a preliminary matter, it is well established that claim language is not required to be described in *ipsis verbis* in the Specification to satisfy the description requirement of 35 U.S.C. § 112. *See, e.g., In re Lukach,* 442 F.2d 967 (CCPA 1971); *Henry J. Kaiser Col. v. McLouth Steel Corp.,* 257 F. Supp. 372 (E.D. Mich. 1966). The test for new matter is whether the application as filed clearly conveys to those of ordinary skill in the art that Applicants invented a method in which analyzing occurs over the period specified in the claims. See, e.g., *In re Wertheim*, 541 F.2d 257, 265 (CCPA 1976). Applicants submit that the above-captioned application clearly conveys to those of ordinary skill in the art that Applicants invented a method in which analyzing occurs over a period of seconds, a period of at least 15 seconds and a period of at least 30 seconds. Examples 1-4 and FIGS. 1A, 2A 3A and 4A of the above-captioned application provide the requisite support. Example 1 and FIG. 1A reflect the analysis of fluctuations in fluorescence that are due to the movement of two pathogens, i.e., bacteria, through a confocal detection volume over a period of seconds; Example 2 and FIG. 2A reflect the analysis of fluctuations in fluorescence due to the movement of a pathogen, e.g., a single bacterium, through a confocal detection volume in a period of less than 30 seconds; Example 4 and FIG. 4A reflect analyzing fluctuations of fluorescence due to the movement of a pathogen, e.g., a single bacterium, through a confocal detection volume in a period of less than 15 seconds. Applicants submit, therefore, that the time periods set forth in claims 132-137 are disclosed in Applicants' Specification. Since claims 132-137 satisfy the written description requirement under 35 U.S.C. § 112, first paragraph, Applicants respectfully request that the rejection be withdrawn.

Claims 59-66 and 118-138 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement.

Claim 59 is directed to a method of assaying for a pathogen that includes exciting a sample with radiation, the sample including a least one pathogen, at least one probe, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the exited sample and analyzing the fluctuations of the fluorescence due to diffusion or flow of the pathogen through the subvolume. Methods for developing probes to pathogens are known. Applicants' Specification describes such methods at page 30, line 15 – page 31,

line 25. United States Provisional Application No 60/430,273, to which the above-captioned application claims priority, also contains a very detailed explanation of preparing probes for pathogens (see, e.g., pages 5, 6, and 11-17). In addition, the Example section of the Applicants' Specification describes working examples of a number of probe pathogen sets. Applicants' Specification thus enables the skilled artisan to conduct the analysis regardless of the probe or the pathogen. As such, Applicants' Specification satisfies the criteria under 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 60-66 and 118-138 satisfy the written description requirement of under 35 U.S.C. § 112, first paragraph, for at least the same reasons set forth above with respect to claim 59. Accordingly, Applicants respectfully request that the rejection of claims 60-66 and 118-138 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 59, 118-121, 124-126, 130-132, 134 and 136 stand rejected under 35 U.S.C. § 112, second paragraph.

Applicants respectfully request clarification of this rejection. MPEP 2172.01 states:

> A claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. § 112, first paragraph, as not enabling. In re Mayhew, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). See also MPEP § 2164.08(c). Such essential matter may include missing elements, steps or necessary structural cooperative relationships of elements described by the applicant(s) as necessary to practice the invention.
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> In addition, a claim which fails to interrelate essential elements of the invention as defined by applicant(s) in the specification may be rejected under 35 U.S.C. § 112, second paragraph, for failure to point out and distinctly claim the invention. See In re Venezia, 530 F.2d 956, 189 USPQ 149 (CCPA 1976); In re Collier, 397 F.2d 1003, 158 USPQ 266 (CCPA 1968). *But see* Ex parte Nolden, 149 USPQ 378, 380 (Bd. Pat. App. 1965) ("[I]t is not essential to a patentable combination that there be interdependency between the elements of the claimed device or that all the elements operate concurrently toward the desired result");

> Ex parte Huber, 148 USPQ 447, 448-49 (Bd. Pat. App. 1965) (A claim does not necessarily fail to comply with 35 U.S.C. § 112, second paragraph where the various elements do not function simultaneously, are not directly functionally related, do not directly intercooperate, and/or serve independent purposes.)

Applicants' believe that the rejection was intended to be under 35 U.S.C. § 112, first paragraph, in light of the reasoning given at page 11 of the April 26th Office action. Applicants submit that the method of claim 59 is enabled. Applicants further submit that there is no omission that amounts to a gap between steps. Accordingly, the rejection of claims 59, 118-121, 124-126, 130-132, 134 and 136 under 35 U.S.C. § 112, second paragraph, is unwarranted and Applicants respectfully request that it be withdrawn.

Applicants submit that the amendment to claim 60 renders moot the rejection of claim 63 under 35 U.S.C. § 112, first paragraph, and respectfully request that it be withdrawn.

Claim 131 stands rejected under 35 U.S.C. § 112, second paragraph. The April 26th Office action asserts, "[T]he language.. [,] 'identify of said pathogen is unknown,' appears to read upon a mental step." April 26th Office action, page 12. The term "unknown" is well-known throughout all fields of science. It is a common term used to refer to something that is not known. The phrase, "identity of said pathogen is unknown" refers to a fact --not a mental step. The identity of the pathogen in the sample is unknown at the time the method is conducted. Such a sample might be taken, for example, from a city's water supply. In the event that citizens of that city had become sick and the water supply was suspected, one could take a sample of the water, without knowing whether or not it contained a pathogen, and analyze it according to the method of claim 131. In this example, if a pathogen is present, the identity of that pathogen is unknown at the time the method is conducted. Applicants submit that claim 131 satisfies the criteria of 35 U.S.C. § 112, second paragraph, and respectfully request that the rejection of claim 131 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claims 132 and 133 stand rejected under 35 U.S.C. § 112, second paragraph. Claims 132 and 133 are clear and definite. Claims 132 and 133 require the analyzing to occur over a period of seconds. A second is a known unit of time. There is nothing indefinite about a second or a period of seconds. Claims 132 and 133 inform the skilled

artisan that an analysis that does not extend over a period of seconds does not fall within the claim language. In other words, an analysis that occurs in less than a second, or over a period of one second, does not fall within the claims. Likewise, an analysis that occurs over a plurality of seconds falls within the claim. The skilled artisan would readily understand both the term "seconds" and the metes and bounds of the method of claims 132 and 133. Applicants submit, therefore that the rejection of claims 132 and 133 under 35 U.S.C. § 112, second paragraph, is unwarranted and respectfully request that it be withdrawn.

Claims 59-66, 118-125, 127, 128, 130-133 and 138 stand rejected under 35 U.S.C. § 102(e) over Rigler et al. (US 6,582,903 B1).

Rigler et al. disclose a method for identifying one or a small number of molecules in very small volumes (i.e., 10^{-14} to 10^{-17} liters) using a laser excited fluorescence correlation spectroscopy (Rigler et al., col. 3, lines 21-25). Rigler et al. explain that an object of their invention is a method for identifying one or a small number of molecules (*Id.*, col. 1, lines 7-8; see also, col. 1., line 65-col. 2, line 6). (Emphasis added.) Rigler et al. further disclose, "[I]t would be more advantageous if analytic methods were sufficiently sensitive to qualitatively and quantitatively apply directly to single molecules or ensembles of a few molecules" (*Id.* lines 20-23). (Emphasis added.) Rigler et al. are particularly interested in studying the interactions that occur between molecules at the molecular level including biochemical reactions, equilibrium constants, and rate constants of single molecules (*Id.*, col. 5, lines 22-26). According to Rigler et al., the illuminated area of the Rigler et al. device has an approximate dimension of 0.1 μm^2, and the measuring volume of the Rigler et al. device is about 1000 times smaller than the measuring volumes described in the literature (*Id.*, col., 3, lines 28-32). A very small measuring volume is important to Rigler et al. because it allows for the dwell time of a molecule in the measuring volume to be about 1000 times shorter than in conventional systems and thereby enables equilibrium constants and rate constants of specific biological recognition reactions to be measured (*Id.* at lines 47-55). Riger et al. further explain, "[The] ligand [that] is to be observed does not change[,] or changes but hardly[,] its molecular structure during its entering into the measuring compartment and its leaving the same." *Id.*, lines 43-46. Rigler et al. also disclose that they have attained a signal-to-

noise ratio of 1000, which is necessary for measuring single molecules (*Id.*, col. 5, lines 1-3). Rigler et al. further explain that the deterioration of this ratio follows the third power of the increased radius of the measuring volume (r^3). In other words, as the measuring volume increases, the signal-to-noise ratio decreases.

Rigler et al. explain that problems in the art include the fact that the observation element was so large that biologically interesting molecules having low translational diffusion coefficients were present in the observation element for a period of about 50 ms (*Id.*, col. 3, lines 3-5). Such a period, according to Rigler et al., is significantly too large because it causes strong bleaching of the respective dye ligands serving as the luminophore (*Id.* at lines 5-7). The Rigler et al. method relies on frequent excitation of the luminophore. According to Rigler et al., frequent excitation increases the chemical reactivity of the luminophorous structure towards molecules of the environment, in particular oxygen, whereby the luminescence is altered or quenched (*Id.* at lines 7-11). Rigler et al. refer to this as photobleaching and further explain that photobleaching leads to false measuring data (*Id.* at lines 11-14). Rigler et al. also disclose that the measuring period over which their analysis is conducted is no greater than 500 milliseconds (ms) (see *Id.*, Abstract), and that the average dwell time for the small volume elements of their invention is less than 1 millisecond (*Id.*, col. 7, lines 23-25). Rigler et al. further explain that the average measuring time for one measurement ranges between 10 ms and 100 ms, which enables specific biological interactions to be measured (*Id.*, lines 51-59).

In distinguishing their method from a cell sorter, Rigler et al. explain that on the level of a cell, their method is able to distinguish between different molecules bearing chromophores and being present in the measuring volume, whereas in the cell sorter the concentration of the chromophore is determined irrespective of whether it is part of a small molecule, occurs in a complex or is bound to a cell (*Id.*, col. 12, lines 54-61). Rigler et al. go on to explain that for slowly diffusing complexes such as cell cultures or tissues, the translational diffusion of the complexes is irrelevant for the analysis (*Id.*, col. 21, lines 56-62). In other words, the complex appears as if it is stationary, i.e., it is effectively stationary, for purposes of the Rigler et al. analysis.

> Surprisingly, even cells can be measured in aqueous suspension despite their large masses. Brownian motion and turbulences are sufficiently high to move,

> e.g., a membrane segment with its receptors[,] into the measuring volume and out again without intervening bleaching phenomena of the dye labels occurring. Schematic FIG. 5 depicts the measurement of nearly stationary molecules according to the invention. As indicated by the rectangle, for instance, they may be present as membrane receptors on an immobilized cell (rectangle). The coordinate axes illustrate the analysis, according to the invention, of non-fluctuating molecules as well by forced relative motion of the measuring volume with respect to the stationary element. This can be done by a relative change of the laser coordinates, of the coordinates of the measuring volume, or of the coordinates of the sample volume, or of a combination thereof.
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> The procedure described according to the invention is possible in the case that the time of translational diffusion of the slowly diffusing complex is irrelevant for analysis and rather the absolute or relative number of the dye labels linked thereto is of interest. This is the case, for instance, in determining receptor binding constants on cell cultures or in tissues.

Id., col. 21, lines 22-61

Claim 59 is directed to a method of assaying for a pathogen that includes exciting a sample with radiation, the sample including a least one pathogen, at least one probe, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the exited sample and analyzing the fluctuations of the fluorescence due to diffusion or flow of the pathogen through the subvolume. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. 2131. Rigler et al. seek to analyze single molecules. Rigler et al. are not interested in analyzing pathogens. A pathogen is an organism. Applicants' Specification expressly lists a pathogen as an example of an organism (See, e.g., Applicants' Specification, page 33, lines 5-6). This is clear evidence from the record that Applicants intended the term "pathogen" to refer to an organism. Since the lack of this evidence was the only basis on which the rejection of claim 59 under 35 U.S.C. § 102(e) over Rigler et al. was maintained, and this evidence is clearly of the record,

Applicants submit that the rejection of claim 59 under 35 U.S.C. § 102(e) over Rigler et al. has been overcome and respectfully request that it be withdrawn.

The Rigler et al. reference is further deficient for at least the following additional reasons. Although Rigler et al. mention viruses and bacteria, Rigler et al. are interested in the interactions of molecules (*see, e.g.,* Rigler et al., col. 1, lines 7-8; see also, col. 1., line 65-col. 2, line 6). This is demonstrated by Rigler et al.'s various discussions pertaining to cells. In particular, Rigler et al. disclose that they are interested in the receptors on membrane segments of cells, (*see, Id.*, col. 21, lines 24-27), as well as receptor binding constants on cell cultures or in tissues (*see, Id.*, col. 21, lines 59-61). In the system depicted in FIG. 5 of Rigler et al., e.g., the cell is immobilized (*see, Id.*, lines 29-31). Rigler et al. are interested in activity that is happening at the receptors of the cell and analyzes various segments of the membrane to study this activity. Thus, the mere use of the terms "pathogen," "virus" and "bacterium" in Rigler et al. does not constitute a teaching of a method that includes analyzing the fluctuations of the fluorescence due to diffusion or flow of a pathogen through a subvolume. To the contrary, many things associated with a pathogen, virus, or bacterium could theoretically be analyzed. Rigler et al. must expressly teach analyzing the fluctuations of the fluorescence due to the diffusion or flow of a pathogen through a subvolume to establish a case of *prima facie* anticipation, and they do not. Nothing in the record establishes anything to the contrary. Accordingly, the rejection of claim 59 under 35 U.S.C. § 102(e) over Rigler et al. cannot stand and Applicants respectfully request that it be withdrawn.

Claims 60-66, 118-125, 127, 128 and 130-133 are distinguishable under 35 U.S.C. § 102(e) over Rigler et al. for at least the same reasons set forth above in distinguishing claim 59.

Claims 60, 65, 66, 130, 132 and 133 are further distinguishable under 35 U.S.C. § 102(e) over Rigler et al. for at least the following additional reasons.

Claim 60 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen, and

determining the presence or absence of the pathogen. As established above, Rigler et al. do not teach assaying for the presence of a pathogen in a sample. Rigler et al. also do not teach analyzing fluctuations of fluorescence that are due to the diffusion or flow of a pathogen. Moreover, Rigler et al. do not teach determining the presence or absence of the pathogen in a sample. Rigler et al. discuss analyzing the DNA or RNA of pathogens. The DNA and RNA of a pathogen are not pathogens. Pathogens are organisms (see, e.g., Applicants' Specification, page 33, lines 5-6). Rigler et al. thus fail to teach the method of claim 60.

Claim 65 depends from claim 1 and specifies that the pathogen includes a bacterium. Rigler et al. do not teach analyzing fluctuations of fluorescence that are due to the diffusion or flow of a bacterium through a subvolume. Rather, Rigler et al. analyze the interaction of molecules in their subvolume and, in particular, the binding constants of molecules, equilibrium constants of molecules, dissociation rate constants of complexes, and conformational changes in biological macromolecules. Rigler et al. expressly disclose that their method is for the fluorescence spectroscopy of single molecules, molecular complexes and molecular fragments (Rigler et al., col. 6, lines 8-11) and further expressly admonish that because single molecules, molecular complexes and molecular fragments are their target, it is "critical ... that there be a confocally located pinhole aperture having an extremely small orifice in the beam path of the [excitation] radiation." *Id.*, lines 11-15. Rigler et al. thus not only fail to teach analyzing fluctuations of fluorescence that are due to the diffusion or flow of a bacterium through their subvolume, but also provide no reason to the skilled artisan to do so. For at least these additional reasons, the rejection of claim 65 under 35 U.S.C. § 102(e) over Rigler et al. is unwarranted and Applicants respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action indicate, by reference to column and line number, the location in Rigler et al. of a teaching of the method of claim 65.

Claims 66 and 130 are further distinguishable under 35 U.S.C. § 102(e) over Rigler et al. for at least the additional reasons set forth above in distinguishing claim 65.

Claim 132 depends from claim 59 and further specifies that the analyzing occurs over a period of seconds. The measuring period over which the Rigler et al. analysis is

conducted is no greater than 500 milliseconds (see Rigler et al.., Abstract). Rigler et al. further disclose that he average measuring time for one measurement ranges between 10 ms and 100 ms. Rigler et al. also explain that the average dwell time in the subvolume for complexes of interest to them is less than 1 millisecond, and that for virtually all of the complexation reactions of interest to them, the complex will remain stable throughout its dwelling time in the measuring volume (*Id.*, col. 7, lines 23-27). Rigler et al. do not teach analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen and further fail to teach conducting such analyzing over a period of seconds. Nothing in the record establishes anything to the contrary. Rigler et al. thus fail to teach a required element of the method of claim 132. Thus claim 132 is further distinguishable under 35 U.S.C. § 102(e) over Rigler et al. for at least this additional reason; Accordingly, the rejection of claim 132 under 35 U.S.C. § 102(e) over Rigler et al. must be withdrawn.

Claim 133 is further distinguishable under 35 U.S.C. § 102(e) over Rigler et al. for at least the same reasons set forth above in distinguishing claim 132.

Claim 138 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting the sample with radiation, the sample including a plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding to a unique pathogen, and measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence, and determining the presence or absence of at least one pathogen. Rigler et al. do not teach a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen, as required by claim 138. Nothing in the record establishes anything to the contrary. Rigler et al. thus fail to teach each and every element of the method of claim 138, and a *prima facie* case of anticipation of claim 138 has not been made. Accordingly, the rejection of claim 138 under 35 U.S.C. § 102(e) over Rigler et al. cannot stand and Applicants respectfully request that it be withdrawn.

Claims 62 and 118 are further distinguishable under 35 U.S.C. § 102(e) over Rigler et al. for at least the same reasons set forth above in distinguishing claim 138.

Claims 59-66, 118-125, 127, 128, 130-133 and 138 stand rejected under 35 U.S.C. § 102(b) over Rigler (Journal of Biotechnology, vol. 41 (1995), pp. 177-186).

Rigler discloses methods for analyzing molecular interactions between ligands and target molecules by exciting a sample to fluorescence with a laser beam and correlating the fluctuations of molecular intensity. Rigler indicates that FCS can be used to examine molecular interactions such as hybridization between nucleic acid primers and DNA or RNA targets, between peptide ligands and cell-bound receptors, and between antigen and antibodies (see, e.g., Rigler, Abstract). Rigler describes the detection of a typical biological interaction of a fluorescence labeled DNA primer of 18 nucleotides binding to a target DNA molecule, namely single stranded M13 bacteriophage DNA (*Id.*, page 178-179).

Claim 59 is directed to a method of assaying for a pathogen that includes exciting a sample with radiation, the sample including a least one pathogen, at least one probe, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the exited sample and analyzing the fluctuations of the fluorescence due to diffusion or flow of the pathogen through the subvolume. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. 2131. Rigler is directed to single molecule detection (see, e.g., Rigler, Title). Rigler explains that the improvements in fluorescence correlation spectroscopy have allowed single molecules to be recorded in fractions of milliseconds (*Id.*, page 177-178). Rigler is interested in interactions between ligands and target molecules (*Id.*, page 178). Rigler describes analyzing free and DNA-bound primer. DNA-bound primer is not a pathogen. A pathogen is an organism. DNA- bound primer is not an organism. Applicants' Specification expressly lists a pathogen as an example of an organism (See, e.g., Applicants' Specification, page 33, lines 5-6). This is clear evidence from the record that Applicants intended the term "pathogen" to refer to an organism. Since the lack of this evidence was the only basis on which the rejection of claim 59 under 35 U.S.C. § 102 over Rigler was maintained, and this evidence is clearly of the record, Applicants submit that the rejection of claim 59 under 35 U.S.C. § 102 over Rigler has been overcome and respectfully request that it be withdrawn.

The Rigler reference is further deficient for at least the following additional reasons. Rigler does not teach analyzing the fluctuations of fluorescence due to diffusion or flow of a pathogen through a subvolume and is not interested in doing so. Rigler thus

fails to teach a required element of the method of claim 59. Accordingly, the rejection of claim 59 under 35 U.S.C. § 102(b) over Rigler cannot stand and Applicants respectfully request that it be withdrawn.

Claims 60-66, 118-125, 127, 128, 130-133 and 138 are distinguishable under 35 U.S.C. § 102(b) over Rigler for at least the same reasons set forth above in distinguishing claim 59.

Claims 62, 65, 66, 118, 130, 132, 133, and 138 are further distinguishable over Rigler for at least the following additional reasons.

Claim 65 depends from claim 1 and specifies that the pathogen comprises a bacterium. Rigler does not teach a bacterium. Rigler also does not analyze fluctuations of fluorescence that are due to the diffusion or flow of a bacterium through a subvolume. Rigler is directed to single molecule detection (see, e.g., Rigler, Title). Rigler explains that the improvements in fluorescence correlation spectroscopy have allowed single molecules to be recorded in fractions of milliseconds (*Id.*, page 177-178). Rigler is interested in interactions between ligands and target molecules. *Id.*, page 178. Rigler describes analyzing free and DNA-bound primer. Rigler does not teach analyzing the fluctuations of fluorescence due to diffusion or flow of a pathogen through a subvolume and is not interested in doing so. Rigler thus fails to teach a required element of claim 65. Nothing in the record refutes this fact. Accordingly, a *prima facie* case of anticipation of claim 65 has not been made and the rejection of claim 65 under 35 U.S.C. § 102(b) over Rigler cannot stand. Applicants respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action indicate, by reference to page and line number, the location in Rigler of a teaching of analyzing the fluctuations in fluorescence due to the diffusion or flow of a bacterium through a subvolume.

Claims 66 and 130 are further distinguishable under 35 U.S.C. § 102(b) over Rigler for at least the additional reasons set forth above in distinguishing claim 65.

Claim 132 depends from claim 59 and further specifies that the analyzing occurs over a period of seconds. The fluorescence correlation spectroscopy system of Rigler includes an illuminated and detected volume of 0.2 femtoliters (Rigler, page 178, second column). Rigler discloses that a single organic dye molecule, when excited to

fluorescence, can be recorded in fractions of milliseconds (Rigler, page 178). Rigler also disclose that a single Rhodamin 6G molecule can be detected within 100 microseconds and less (*Id.*, page 181, first column). Rigler also explains that an autocorrelation function can be obtained within 0.1 second when a ligand labeled receptor is present in a concentration of 1 nanomole. Figure 7 of Rigler depicts obtaining the autocorrelation function of M13-DNA over a period of less than 300 seconds. Rigler further explains that for particles with diffusion coefficients and diffusion times similar to those of M13 bacteriophage DNA, the detection time will be a limiting factor if particle detection rests on thermal motion only. To solve this problem, Rigler discloses using electric field gradients to achieve an analysis time of less than 100 microseconds (*Id.*, page 183). Rigler thus teaches away from analyzing fluctuations in fluorescence due to the diffusion over a period seconds. Nothing in the record establishes anything to the contrary. Rigler thus also fails to teach this additional element of the method of claim 132. Accordingly, a *prima facie* case of anticipation of claim 132 has not been made. Thus the rejection of claim 132 under 35 U.S.C. § 102(b) over Rigler cannot stand and must be withdrawn.

Claim 133 is further distinguishable under 35 U.S.C. § 102(b) over Rigler for at least the same reasons set forth above in distinguishing claim 132.

Claim 138 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting the sample with radiation, the sample including a plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding to a unique pathogen, and measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence, and determining the presence or absence of at least one pathogen. Rigler does not teach a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen, as required by claim 138. Nothing in the record establishes anything to the contrary. Rigler thus fails to teach each and every element of the method of claim 138. Accordingly, a *prima facie* case of anticipation of claim 138 has not been made. Applicants submit, therefore, that the rejection of claim 138 under 35 U.S.C. § 102(b) over Rigler cannot stand, and respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action include a reference, by page and column, to the

location in Rigler of a teaching of a sample including a plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding to a unique pathogen.

Claims 62 and 118 are further distinguishable under 35 U.S.C. § 102(b) over Rigler for at least the same reasons set forth above in distinguishing claim 138.

Claims 59-66, 118-125, 127, 128, 130-133 and 138 stand rejected under 35 U.S.C. § 102(b) over Weiner et al. (Digestion, 2000, vol. 61, pp. 84-89).

Weiner et al. disclose methods for combining an amplification technique, namely the PCR, with fluorescence correlation spectroscopy to quantify levels of pathogenic hepatitis C virus RNA in clinical samples. More specifically, Weiner et al. describe extracting HCV RNA from human serum, and performing cDNA synthesis and PCR using a Cy3-labeled fluorescent probe to HCV RNA. Weiner et al. also disclose diluting the PCR mixtures, denaturing the mixtures to resolve nonspecific binding of the fluorescence-labeled probes, and analyzing the crude PCR mixtures with an argon-ion laser fluorescence correlation spectrometer to determine the amount of fluorescence-labeled nucleic acids for identification of the virus.

Claim 59 is directed to a method of assaying for a pathogen in a sample where the sample includes a least one pathogen, at least one probe, and at least one fluorescent tag. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. 2131. Weiner et al. disclose a method of using fluorescence correlation spectroscopy to measure levels of hepatitis C virus RNA, which is a macromolecule. A pathogen is an organism. The RNA of hepatitis C virus is not an organism. The RNA of hepatitis C virus also does not cause a disease state. Thus, the RNA of hepatitis C virus is not a pathogen. Therefore, Weiner et al. do not teach a sample that includes a pathogen. Nothing in the record establishes anything to the contrary. Applicants' Specification expressly lists a pathogen as an example of an organism (See, e.g., Applicants' Specification, page 33, lines 5-6). This is clear evidence from the record that Applicants intended the term "pathogen" to refer to an organism. Since the lack of this evidence was the only basis on which the rejection of claim 59 under 35 U.S.C. § 102 over Weiner et al. was maintained, and this evidence is clearly of the record, Applicants submit that the

rejection of claim 59 under 35 U.S.C. § 102 over Rigler has been overcome and respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action indicate, by reference to page and line number, the location in Weiner et al. of a teaching of a sample that includes a pathogen.

The Weiner et al. reference is further deficient for at least the following additional reason. Weiner et al. do not teach analyzing the fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume of the sample. Weiner et al. thus fail to teach required elements of the method of claim 59. For at least this additional reason the rejection of claim 59 under 35 U.S.C. § 102(b) over Weiner et al. is unwarranted, and Applicants respectfully request that it be withdrawn.

Claims 118-121, 124, 125, and 130-133 are distinguishable under 35 U.S.C. § 102(b) over Weiner et al. for at least the same reasons set forth above in distinguishing claim 59.

Claim 60 is directed to a method of assaying for the presence of a pathogen in a sample where the method includes exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen through the subvolume, and determining the presence or absence of the pathogen. Weiner et al. do not teach a method of assaying for the presence of a pathogen. Rather, Weiner et al. disclose a method of using fluorescence correlation spectroscopy to measure levels of hepatitis C virus RNA, which is a macromolecule. The RNA of hepatitis C virus does not produce a disease. The RNA of hepatitis C virus thus is not a pathogen. Weiner et al. also do not analyze the fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume. Rather, Weiner et al. analyze the diffusion of RNA. Weiner et al. also do not teach determining the presence or absence of a pathogen in a sample. Weiner et al. thus fail to teach each and every element of the method of claim 60. Accordingly, Applicants submit that the rejection of claim 60 under 35 U.S.C. § 102(b) over Weiner et al. has been overcome and respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that

the next action indicate, by reference to page and line number, the location in Weiner et al. of a teaching of determining the presence or absence of a pathogen in a sample.

Claims 61-66, 122, 123, 127, 128 are distinguishable under 35 U.S.C. § 102(b) over Weiner et al. for at least the same reasons set forth above in distinguishing claim 60.

Claim 65 depends from claim 60 and specifies that the pathogen comprises a bacterium. Weiner et al. disclose a method of using fluorescence correlation spectroscopy to measure levels of hepatitis C virus RNA, which is a macromolecule. The RNA of hepatitis C virus is not a bacterium. Thus, Weiner et al. do not teach a bacterium. Nothing in the record establishes anything to the contrary. Weiner et al. also do not analyze fluctuations of fluorescence that are due to the diffusion or flow of a bacterium through a subvolume. Nothing in the record establishes anything to the contrary. Weiner et al. thus fail to teach a required element of claim 65. Accordingly, a *prima facie* case of anticipation of claim 65 has not been made. Applicants submit, therefore, that the rejection of claim 65 under 35 U.S.C. § 102(b) over Weiner et al. cannot stand, and respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action indicate, by reference to page and line number, the location in Weiner et al. of a bacterium, as well as a teaching of analyzing the fluctuations in fluorescence due to diffusion or flow of a bacterium.

Claim 66 depends from claim 60 and specifies that the pathogen comprises a virus. Weiner et al. disclose a method of using fluorescence correlation spectroscopy to measure levels of hepatitis C virus RNA, which is a macromolecule. The RNA of hepatitis C virus is not a virus. Thus, Weiner et al. do not teach a virus. Nothing in the record establishes anything to the contrary. Weiner et al. also do not analyze fluctuations of fluorescence that are due to the diffusion or flow of a virus through a subvolume. Nothing in the record establishes anything to the contrary. Weiner et al. thus fail to teach a required element of claim 66. Accordingly, a *prima facie* case of anticipation of claim 66 has not been made. Applicants submit, therefore, that the rejection of claim 66 under 35 U.S.C. § 102(b) over Weiner et al. cannot stand, and respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action indicate, by reference to page and line number, the location in Weiner et

al. of a teaching of a virus and analyzing the fluctuations in fluorescence due to the diffusion or flow of a virus.

Claim 130 is further distinguishable under 35 U.S.C. § 102(b) over Weiner et al. for at least the additional reasons set forth above in distinguishing claims 65 and 66.

Claim 132 depends from claim 59 and further specifies that the analyzing occurs over a period of seconds. Weiner et al. do not teach analyzing fluctuations in fluorescence due to diffusion or flow of a pathogen over a period of seconds. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of obviousness of claim 132 has not been made and the burden has not shifted to Applicants to rebut the same. Applicants submit, therefore, that the rejection of claim 132 under 35 U.S.C. § 102(b) over Weiner et al. is unwarranted and respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action indicate, by reference to page and line number, the location in Weiner et al. of a teaching of analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen over a period of seconds.

Claims 133-137 are distinguishable under 35 U.S.C. § 103 over Weiner et al. for at least the same reasons as set forth above in distinguishing claim 132.

Claim 138 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting the sample with radiation, the sample including a plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding to a unique pathogen, and measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence, and determining the presence or absence of at least one pathogen. Weiner et al. do not teach a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen, as required by claim 138. Nothing in the record establishes anything to the contrary. Weiner et al. thus fail to teach each and every element of the method of claim 138, and a *prima facie* case of anticipation of claim 138 has not been made. Accordingly, the rejection of claim 138 under 35 U.S.C. § 102(b) over Weiner et al. cannot stand and Applicants respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action indicate, by reference to page and line

number, the location in Weiner et al. of a teaching of a sample that includes a plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding to a unique pathogen.

Claims 59-66, 118-125, 127, 128, 130-133 and 138 stand rejected under 35 U.S.C. § 102(b) Walter et al. (Proc. Natl. Acad. Sci., USA, November 1996, vol. 93, pp. 12805-12810).

Walter et al. discuss methods for combining an amplification technique, namely the PCR, with fluorescence correlation spectroscopy to detect the specific *in vitro* amplifications of the genomic sequence of a bacterium. Walter et al. describe using at least one primer, a rhodamine-labeled fluorescent probe, and *Mycobacterium tuberculosis* genomic DNA as a target. Walter et al. disclose various combinations of primer/probe concentrations during PCR amplification of a target sequence specific for the *M. tuberculosis* sequence for effective products. Walter et al. also disclose the use of fluorescence correlation spectroscopy to measure the diffusion times of fluorescently labeled nucleic acids.

As set forth above, claim 59 is directed to a method of assaying for a pathogen in a sample that includes a least one pathogen, at least one probe, and at least one fluorescent tag. The method of claim 59 also includes analyzing the fluctuations of the fluorescence due to diffusion or flow of the pathogen through the subvolume. Walter et al. do not teach a sample that includes a pathogen. To the contrary, Walter et al. disclose combining an amplification technique, namely PCR, with an FCS-based detection technique and testing the method with different primer/probe combinations on *Mycobacterium tuberculosis* genomic DNA as a target (Walter et al., Abstract). (Emphasis added.) A pathogen is an organism. The genomic DNA of *Mycobacterium tuberculosis* is not an organism and does not produce a disease; therefore it is not a pathogen. Applicants' Specification expressly lists a pathogen as an example of an organism (See, e.g., Applicants' Specification, page 33, lines 5-6). This is clear evidence from the record that Applicants intended the term "pathogen" to refer to an organism. Since the lack of this evidence was the only basis on which the rejection of claim 59 under 35 U.S.C. § 102 over Walter et al. was maintained, and this evidence is clearly of

the record, Applicants submit that the rejection of claim 59 under 35 U.S.C. § 102 over Rigler has been overcome, and respectfully request that it be withdrawn.

The Walter et al. reference is further deficient for at least the following additional reason. Walter et al. do not analyze the fluctuations of the fluorescence due to diffusion or flow of the pathogen through the subvolume. Rather, Walter et al. measure the diffusion times of fluorescently labeled nucleic acids and probe extensions. Walter et al. thus fail to teach each and every element of the method of claim 59. Applicants submit, therefore, that the rejection of claim 59 under 35 U.S.C. § 102(b) over Walter et al. is unwarranted and respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action indicate, by reference to page and line number, the location in Walter et al. of a teaching of a sample that includes a pathogen.

Claims 118-121, 124, 125, and 130-133 are distinguishable under 35 U.S.C. § 102(b) over Walter et al. for at least the same reasons set forth above in distinguishing claim 59.

Claim 60 is now directed to a method of assaying for the presence of a pathogen in a sample where the method includes exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen through the subvolume, and determining the presence or absence of the pathogen. Walter et al. do not assay for the presence of a pathogen. Rather, Walter et al. analyze properties associated with probe extensions that result from hybridization. Walter et al. also do not teach analyzing fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume. Rather, Walter et al. analyze fluctuations in fluorescence associated with fluorescently labeled nucleic acids and probe extensions. Nucleic acids and probe extensions are not pathogens. Nucleic acids and probe extensions are not organisms and do not inherently produce a disease state. Walter et al. thus not only fail to teach a pathogen, but also fail to teach analyzing fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume. Walter et al. also do not teach determining the presence or absence of a pathogen in a sample.

Walter et al. thus fail to teach each an every element of the method of claim 60. Accordingly, the rejection of claim 60 under 35 U.S.C. § 102(b) over Walter et al. has been overcome and Applicants respectfully request that it be withdrawn.

Claims 61-66, 122, 123, 127, 128 are distinguishable under 35 U.S.C. § 102(b) over Walter et al. for at least the same reasons set forth above in distinguishing claim 60.

Claim 65 depends from claim 60 and specifies that the pathogen comprises a bacterium. Walter et al. analyze properties associated with probe extensions that result from hybridization. A probe extension that results from hybridization is not inherently a bacterium. Thus, Walter et al. do not teach a bacterium. Walter et al. also do not analyze fluctuations of fluorescence that are due to the diffusion or flow of a bacterium through a subvolume. Nothing in the record establishes anything to the contrary. Walter et al. thus fail to teach a required element of claim 65. Accordingly, a *prima facie* case of anticipation of claim 65 has not been made. Applicants submit, therefore, that the rejection of claim 65 under 35 U.S.C. § 102(b) over Walter et al. cannot stand, and respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action indicate, by reference to page and line number, the location in Walter et al. of a teaching of a bacterium and analyzing the fluctuations in fluorescence due to diffusion or flow of a bacterium.

Claim 66 depends from claim 60 and specifies that the pathogen comprises a virus. Walter et al. analyze properties associated with probe extensions that result from hybridization. A probe extension that results from hybridization is not inherently a virus. Thus, Walter et al. do not teach a virus. Walter et al. also do not analyze fluctuations of fluorescence that are due to the diffusion or flow of a virus through a subvolume. Nothing in the record establishes anything to the contrary. Walter et al. thus fail to teach a required element of claim 66. Accordingly, a *prima facie* case of anticipation of claim 66 has not been made. Applicants submit, therefore, that the rejection of claim 66 under 35 U.S.C. § 102(b) over Walter et al. cannot stand, and respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action indicate, by reference to page and line number, the location in Walter et al. of a teaching of a virus and analyzing the fluctuations in fluorescence due to diffusion or flow of a virus.

Claim 130 is further distinguishable under 35 U.S.C. § 102(b) over Walter et al. for at least the additional reasons set forth above in distinguishing claims 65 and 66.

Claim 138 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting the sample with radiation, the sample including a plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding to a unique pathogen, and measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence, and determining the presence or absence of at least one pathogen. Walter et al. do not teach a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen, as required by claim 138. Walter et al. also do not teach determining the presence or absence of at least one pathogen. Nothing in the record establishes anything to the contrary. Walter et al. thus fail to teach each and every element of the method of claim 138, and a *prima facie* case of anticipation of claim 138 has not been made. Accordingly, the rejection of claim 138 under 35 U.S.C. § 102(b) over Walter et al. cannot stand and Applicants respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action indicate, by reference to page and line number, the location in Walter et al. of a teaching of a sample that includes a plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding to a unique pathogen.

Claims 59-66, 118-125, 127, 128, 130-133 and 138 stand rejected under 35 U.S.C. § 103 over Kask (US 6,515,289) in view of Lahiri et al., (US 2003/0138853 A1).

Kask discloses methods for detecting substances in a sample or measuring the interaction or reaction of substances in a sample. Kask specifically describes a method of identifying nucleic acid strands by a labeled probe molecule. Kask explains using a mixture of primers labeled with dyes of different brightness to identify a target nucleic acid. Kask discloses monitoring intensity fluctuations of radiation emitted by the molecules or particles in at least one measurement volume, determining intermediate statistical data, and determining a distribution of molecules or particles as a function of at least two specific physical properties of the intermediate statistical data.

Lahiri et al. disclose an array that includes a plurality of biological membrane microspots on a surface of a substrate. The microspots include a protein bound to the membrane (Lahiri et al., [0006]). The method of Lahiri et al can be used for detecting a binding event between a probe array and target compounds (*Id.* at [0023]). Lahiri et al. explain that the array can be interfaced with optical detection methods (*Id.* at [0071]).

Claim 59 is directed to a method of assaying for a pathogen in a sample. The method includes exciting a sample with radiation, measuring the fluorescence from a subvolume of the sample, and analyzing the fluctuations of the fluorescence due to the diffusion or flow of the pathogen through the subvolume, where the sample includes a least one pathogen, at least one probe, and at least one fluorescent tag. To establish a *prima facie* case of obviousness based upon a proposed combination of references there must be a reason in the prior art to combine the references. See, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. _____ (2007). Evidence of a reason to combine can be found if there is a teaching, suggestion or motivation in the prior art for making the proposed combination. See, M.P.E.P. 2142; *Fromson v. Anitec Printing Plates, Inc.*, 132 F.3d 1437 (Fed. Cir. 1997); *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, (Fed. Cir. 1998). The reason, teaching, suggestion or motivation to make the claimed combination must be found in the prior art and must not be based on Applicant's disclosure. See, M.P.E.P. 2142. Here there is no such reason, teaching, suggestion or motivation.

It is undisputed that Kask fails to teach a sample that includes a pathogen (see April 26th Office action, page 23). Kask is further deficient in that he also does not teach analyzing the fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume. The method of Kask requires monitoring intensity fluctuations of radiation emitted by molecules or particles. The Kask method characterizes a sample on the basis of intermediate statistical data. The focus of Kask is on his intermediate statistical function. Kask seeks to utilize his function for measuring slight differences in the physical properties of various species. Kask discloses a number of specific physical properties that can characterize a "unit," including absorption cross-section, quantum yield of fluorescence, diffusion coefficient, correlation time of radiation intensity fluctuations, any other property expressing how fast or slow Brownian motion of a given unit is, specific brightness, polarization ratio, anisotropy, any other property expressing

the extent of polarization of fluorescence, lifetime of fluorescence, and ratio of fluorescence intensity passing through different optical filters. See, e.g., Kask, col. 3, lines 53-62, col. 6, line 55-col. 7, line 36. Kask does not direct the skilled artisan to select any particular specific physical property from this long list of properties for use in characterizing any particular unit.

Kask then provides a laundry list of "units," which includes "particles, molecules, aggregates, vesicles, cells, viruses, bacteria, centers or mixtures thereof in solids, liquids or gases." *Id.*, col. 6, lines 31-34. Although Kask mentions that the units can be bacteria or viruses, Kask does not teach or suggest characterizing a virus or bacterium with any specific physical property. In particular, Kask does not teach that the specific physical property to select to characterize a virus or bacterium is analyzing the fluctuations in fluorescence due to the diffusion or flow of a bacterium or virus through a subvolume. Kask also does not provide any reason or motivation to the skilled artisan to decide to analyze the fluctuations in fluorescence due to the diffusion or flow of a bacterium or a virus through a subvolume. All of the examples and all of the claims of Kask involve analyzing radiation emitted by molecules. None of the examples of Kask involve analyzing bacteria or viruses in general or analyzing the diffusion or flow of a bacterium or virus in particular. In the background section and throughout the patent, Kask explains that fluorescence correlation spectroscopy is for use in studying molecules. Kask also discuses uses of his method, all of which involve analyzing molecular interactions. For example, with respect to cells and vesicles, Kask discloses,

> [S]ubstances that are possibly pharmacologically active can be analyzed through their interaction with specific receptors by examining said interaction with binding of a luminescently labeled ligand to receptors wherein natural receptors on their carrier cells as well as receptors on receptor-overexpressing carrier cells or receptors on vesicles or receptors in the form of expressed molecules or molecular complexes may be used.

Kask, col. 7, lines 43-50.

In the above-quoted passage, Kask does not teach analyzing the fluctuations in fluorescence due to the diffusion of the cell or vesicle. Rather, Kask is interested in interactions with receptors on the cell or vesicle. The above-quoted passage thus

demonstrates that Kask is looking at interactions that are occurring at the molecular level. Nothing in Kask directs the skilled artisan to analyze fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume.

Lahiri et al. do not cure the deficiencies of Kask. The focus of Lahiri et al. is on arrays of biological membranes. Lahiri et al. disclose that their biological membrane array can be interfaced with a number of detection methods (see, Lahiri et al., para. [0071]). Lahiri et al. then provide a long list of optical detection methods. See, *Id.* Fluorescence correlation spectroscopy is one of the many optical detection methods listed by Lahiri et al. Lahiri et al. refer to fluorescence correlation spectroscopy as an example of a detection method –not an analysis method. This is consistent with the nature of the samples of Lahiri et al., which are biological membranes to which a protein is bound, i.e., the protein is not mobile and therefore cannot diffuse or flow (see, e.g., Lahiri et al., para. [0037]). Lahiri et al. describe contacting an array with a sample that includes a protein and then detecting the protein in the sample that is retained at each microspot, i.e., a membrane bound to a substrate, of the array. *Id.*, para. [0074]. Lahiri et al. do not teach or suggest analyzing fluctuations in fluorescence due to diffusion. Moreover, Lahiri et al. provide the skilled artisan with no reason to analyze fluctuations in fluorescence due to diffusion, because the target molecules become immobilized on the array in the Lahiri et al. method. For at least this reason the skilled artisan familiar with Kask would have no reason to combine Kask and Lahiri et al. in the manner proposed in the April 26th Office action.

The proposed combination of Kask and Lahiri et al. is further deficient for at least the following additional reasons. Lahiri et al. refer to a pathogen at paragraph [0077]. However, this reference is with respect to Lahiri et al.'s biological membrane array, which is the focus of the Lahiri et al. patent. In particular, Lahiri et al. disclose, "The array may be used in a diagnostic manner when the plurality of analytes being assayed are indicative of a disease condition or the presence of a pathogen in an organism." Lahiri et al., [0077]. (Emphasis added.) Lahiri et al. further disclose, "In such embodiments, the sample … [that] is delivered to the array will then typically be derived from a body fluid or a cellular extract from the organism." *Id.* Lahiri et al. do not teach that the sample includes a pathogen. Rather, Lahiri et al. explain that their array can be used when the

analytes being assayed are indicative of a disease condition. Analytes that are indicative of the presence of a pathogen are not necessarily, i.e., inherently, pathogens. Thus, Lahiri et al. do not teach that actual pathogens are being analyzed. Therefore, Lahiri et al. do not expressly teach a sample that includes a pathogen. Accordingly, the proposed combination of Kask and Lahiri et al. lacks a required element of claim 59, i.e., a sample that includes pathogen. Applicants submit, therefore, that the rejection of claim 59 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. is unwarranted and respectfully request that it be withdrawn.

The proposed combination of Kask and Lahiri et al. is further deficient for at least the following additional reasons. Lahiri et al. disclose a number of different types of arrays. Lahiri et al. also list fluorescent correlation spectroscopy as one of many optical detection methods with which their arrays can be interfaced. Nothing in Lahiri et al. specifically directs the skilled artisan to select fluorescent correlation spectroscopy for use in combination with an array for detecting a pathogen or a sample that includes a pathogen. Therefore, the skilled artisan would have no reason to select a fluorescent correlation spectroscopy method over any other method disclosed by Lahiri et al. for use with a sample that includes a pathogen. In addition, in the method of Lahiri et al., the protein in a sample becomes immobilized. Lahiri et al. are concerned with detecting this immobilized protein. Lahiri et al. are not concerned with the diffusion of an analyte --let alone diffusion of a pathogen. Thus, the skilled artisan familiar with Kask would have no reason to modify the method of Kask to include analyzing fluctuations in fluorescence due to diffusion or flow of a pathogen. Moreover, the skilled artisan would not think to do so given the fact that any pathogen detected by Lahiri et al would be immobilized and therefore incapable of diffusing. For at least these additional reasons, Applicants submit that the proposed combination of Kask and Lahiri et al. fails to render obvious the method of claim 59, and respectfully request that the rejection of claim 59 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. be withdrawn.

Claims 60-66 are distinguishable under 35 U.S.C. § 103 over Kask in view of Lahiri et al. for at least the same reasons as set forth above in distinguishing claim 59.

Claims 62, 64, 120, 121, 127, 129 and 132-137 are further distinguishable over Kask in view of Lahiri et al. for at least the following additional reasons.

Claim 62 depends from claim 60 and further specifies that the sample includes a plurality of unique fluorescently tagged probes, each unique probe comprising a unique fluorophore, each unique probe being capable of binding a unique pathogen. Kask does not teach a sample that includes a pathogen, let alone unique probes being capable of binding a unique pathogen. To the contrary, Kask discloses that the dyes all bind to the same target.

Lahiri et al. do not cure the deficiencies of Kask. Accordingly, a *prima facie* case of obviousness has not been made. Applicants submit, therefore, that the rejection of claims 60 and 118 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. is unwarranted and respectfully request that it be withdrawn.

Claim 64 depends from claim 60 and further specifies that the analyzing includes at least one of determining the crosscorrelation function of the sample and determining the autocorrelation function of the sample. Neither Kask nor Lahiri et al. nor the combination thereof teaches or suggests determining either a crosscorrelation function or an autocorrelation function. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of obviousness has not been made and the burden has not shifted to Applicants to rebut the same. Applicants submit, therefore, that the rejection of claims 64, 125 and 128 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. is unwarranted and respectfully request that it be withdrawn.

Claim 120 depends from claim 59 and further specifies that the probe includes multiple binding sites for binding the pathogen. Neither Kask nor Lahiri et al. nor the combination thereof teaches or suggests a probe that includes multiple binding sites for binding a pathogen. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of obviousness of claim 120 has not been made and the burden has not shifted to Applicants to rebut the same. Applicants submit, therefore, that the rejection of claims 120 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. is unwarranted and respectfully request that it be withdrawn.

Claim 121 depends from claim 59 and further specifies that the pathogen includes multiple binding sites for binding the probe. Neither Kask nor Lahiri et al. nor the combination thereof teaches or suggests a pathogen that includes multiple binding sites for binding the probe. Nothing in the record establishes anything to the contrary.

Accordingly, a *prima facie* case of obviousness of claim 121 has not been made and the burden has not shifted to Applicants to rebut the same. Applicants submit, therefore, that the rejection of claims 121 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. is unwarranted and respectfully request that it be withdrawn.

Claim 126 depends from claim 124 and further specifies that the correction algorithm adjusts the measured correlation function based on a bleed through coefficient. Neither Kask nor Lahiri et al. nor the combination thereof teaches or suggests that the correction algorithm adjusts the measured correlation function based on a bleed through coefficient. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of obviousness of claim 126 has not been made and the burden has not shifted to Applicants to rebut the same. Applicants submit, therefore, that the rejection of claim 126 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. is unwarranted and respectfully request that it be withdrawn.

Claim 127 depends from claim 60 and further includes obtaining a measured correlation function of the pathogen and applying a correction algorithm to the measured correlation function. Neither Kask nor Lahiri et al. nor the combination thereof teaches or suggests obtaining a measured correlation function of the pathogen and applying a correction algorithm to the measured correlation function. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of obviousness of claim 127 has not been made and the burden has not shifted to Applicants to rebut the same. Applicants submit, therefore, that the rejection of claim 127 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. is unwarranted and respectfully request that it be withdrawn.

Claim 129 depends from claim 127 and further specifies that the correction algorithm adjusts the measured correlation function based on a bleed through coefficient. Neither Kask nor Lahiri et al. nor the combination thereof teaches or suggests the correction algorithm adjusts the measured correlation function based on a bleed through coefficient. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of obviousness of claim 129 has not been made and the burden has not shifted to Applicants to rebut the same. Applicants submit, therefore, that the rejection of

claim 129 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. is unwarranted and respectfully request that it be withdrawn.

Claim 132 depends from claim 59 and further specifies that the analyzing occurs over a period of seconds. Neither Kask nor Lahiri et al. nor the combination thereof teaches or suggests analyzing over a period of seconds. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of obviousness of claim 132 has not been made and the burden has not shifted to Applicants to rebut the same. Applicants submit, therefore, that the rejection of claim 132 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. is unwarranted and respectfully request that it be withdrawn.

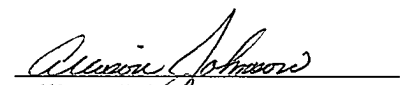
Claims 133-137 are distinguishable under 35 U.S.C. § 103 over Kask in view of Lahiri et al. for at least the same reasons as set forth above in distinguishing claim 132.

The claims now pending in the application are in condition for allowance and such action is respectfully requested.

The Commissioner is hereby authorized to charge any additional fees that may be required and to credit any overpayment to Deposit Account No. 501,171.

Respectfully submitted,

Date: August 24, 2007



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